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(54) Title: A PHARMACEUTICAL COMPOSITION FOR THE ADMINISTRATION OF WATER-INSOLUBLE PHARMACEUTICALLY ACTIVE SUBSTANCES AND A PROCESS FOR PREPARATION THEREOF

(57) Abstract: The pharmaceutical composition in the form of a stable oil-in-water microemulsion prepared in accordance with the process of the invention consists essentially of water-insoluble pharmaceutically active material; C8 to C20 propylene glycol esters of fatty acids of vegetable oils and glyceryl esters of fatty acids or fatty acid vegetable oil glycerides; surfactant; and a hydrophilic phase.

TITLE OF INVENTION

A PHARMACEUTICAL COMPOSITION FOR THE ADMINISTRATION OF WATER-INSOLUBLE PHARMACEUTICALLY ACTIVE SUBSTANCES AND A PROCESS FOR PREPARATION THEREOF

FIELD OF INVENTION

PHARMACEUTICAL DRUG

This invention relates to a pharmaceutical composition for the administration of water-insoluble pharmaceutically active substances and a process for preparation thereof.

There are a number of pharmaceutically active substances which are water-insoluble and which, as a result, present a number of problems for their safe administration and bio-availability. Among such substances, for example, are the cyclosporins, and water-insoluble peptides, antimicrobials and antineoplastics. There have been many proposals of pharmaceutical formulations for the administration of cyclosporins, some of which are described in the following patent specifications: W092/09299, GB-A-2015339,GB-A-2270842, WO94/08610, WO92/18105, GB-A-2228198, U.S.Pat.No.4.388.307, GB-A-2222770, EP-A-0539319 and EP-A-0589843 (Indian references not available).

In general, because the cyclosporins are hydrophobic, pharmaceutical compositions containing them usually comprise lipophilic materials, such as oils. GB-A-2228198 et al, describes, for example, pharmaceutical compositions containing cyclosporin in a carrier medium of a fatty acid triglyceride, a glycerol fatty acid partial ester or propylene glycol or sorbitol complete or partial ester, and a surface active agent having an HLB of at least 10. These oil-based compositions are not intended to be emulsified in water, but are used as such, and are preferably free of ethanol.

Other cyclosporin compositions are known which contain not only hydrophobic oils but also hydrophilic materials such as propylene glycol and ethanol in which cyclosporins are soluble. These compositions are in the form of emulsions. Emulsions have certain advantages over oil-based single phase compositions, and EP-A-0589843 describes some cyclosporin emulsion compositions containing, as the carrier medium, a hydrophilic organic solvents, a mixed monodi-and triglyceride or a transesterified and polyethoxylated vegetable oil, a polyoxyethylene sorbitan-fatty acid ester surfactant, and an aqueous phase. The carrier medium with the cyclosporin but without the aqueous phase is described as an emulsion preconcentrate.

In recent times, microemulsions have been developed for cyclosporin administration and these have provided further advantages over the prior known (coarse) emulsions, especially for oral administration formulations. It is also known to provide so-called "micro-emulsion preconcentrates". For example, GB-A-2222770, describes a pharmaceutical microemulsion preconcentrates composition comprising cyclosporin, a hydrophilic phase, a lipophilic phase and a surfactant. This preconcentrate is converted to a microemulsion by adding water or another suitable adueous medium.

These and other microemulsions for cyclosporins are all made by discovering the cyclosporin in a hydrophilic phase example Propylene glycol, and then mixing the solution with the oil and eventually with an aqueous phase. Applicants have found that there can be a tendency with these microemulsions for solid microfine cyclosporin to be formed during their use, e.g. after administration. This is basically undesirable, and the applicants have found that microemulsions can be made in which this tendency is very much reduced or totally absent.

Summary of the invention:

In, particular, the applicant has found that if the water-insoluble active substance is first dissolved directly in the lipophilic phase, rather than in a hydrophilic phase, and then the oil-in-water microemulsion produced therefrom, the substance remains in solution in the lipophilic (oil) phase. This phase is distributed throughout the aqueous phase of the microemulsions as very tiny particles, and it appears that in this way the substance can be taken up very easily and efficiently by the body. In addition, there is no precipitation of the substances out of the oil solution.

In one aspect, the invention provides a pharmaceutical composition in the form of a stable oil-in-water microemulsion, comprising :

a) a water-insoluble pharmaceutically active material;
b) C8 to C20 propylene glycol esters of fatty acids of vegetable oils and glyceryl esters of fatty acids or fatty acid vegetable oil glycerides;
c) surfactant; and
d) a hydrophilic phase;
e) wherein the said water-insoluble pharmaceutically active material has been wholly directed dissolved in the C8 to C20 propylene glycol esters of fatty acids of vegetable oils and glyceryl esters of fatty acids or fatty acid vegetable oil glycerides, and the said composition is free from ethanol.

Description of the preferred embodiments:

EP-A-327280 describes dissolving cyclosporin in a mono-or di-glyceride of C6-C10 fatty acid. The solution may then be emulsified in an

aqueous medium. However, these emulsions are not microemulsions and do not contain the mixture of lecithin and another surfactant which is especially used, together with the particular triglycerides component (b) all of which are necessary to obtain the significant advantages of the invention.

Microemulsions are transparent due to very small particle size of the dispersed phase, typically less than 200 nm. Such small droplets produce only weak scattering of visible light when compared with that from the coarse droplets (1 - 10 nm) of normal emulsions. An essential difference between microemulsions and emulsions is that microemulsions from spontaneously and, unlike emulsions, required little mechanical work in their formulation. General reviews on microemulsions are provided by Attwood D et al J Colloid Interface Sci 46: 249 and Kahliweit M et al J. Colloid Interface Sci 118:436.

In the present invention, component (a) is a water insoluble pharmaceutically active material. The invention is particularly useful with the cyclosporins, e.g. cyclosporin A, dihydrocyclosporin C, cyclosporin D and dihydrocyclosporin D. It is also useful with other water-insoluble substances such as, taxol.

In the compositions of the invention, component (a) is in solution in component (b). Component (b) can be a single glyceride or any mixture of propylene glycol esters of fatty acid glyceride (mono- and/or di- and/or tri-) derived from vegetable oils and containing C8 to C20 fatty acid residues.

The composition of oil may be as below :

a. Carpylic/Capric triglycerol - Labrafac CC
b. Propylene glycol monocaprylate - Caprgol 90
c. Propylene glycol monolaurate - Lauroglycol 90
d. Glyceryl monolinoleate - Maisine
e. Triglycerides of ricinoleic acid - Castor oil

Component (c) is a surfactant to provide the stable microemulsion. Those skilled in the art will be aware of many surfactants which may be used, but the applicant preferred to use polyoxyl 40 hydrogenated castor oil, polyoxyethylene-sorbitan monooleate, polyoxyethylene-sorbitan monopalmitate, polyoxyethylene-sorbitan monolaurate or polyoxyethylene sorbitan monostearate.

In the microemulsions of the invention, component (d) is a hydrophilic phase. The preferred material is propylene glycol or diethylene glycol monoethyl ether (transcutol) but other substances may be used. Ethanol cannot be present. Water can be present, but it is not preferred. Despite the use of propylene glycol, component (a) remains wholly dissolved in the oil phase [component (b)].

In use, the microemulsion preconcentrates of the invention are diluted with aqueous liquid (e.g. water, fruit juice, milk and the like) to form an oil-in-water microemulsion, e.g. for oral administration. This aids in ready absorption as the surface area of the globules is largely increased. The role played by bile salts in the initial step of fragmentation of fat globules, essential for fat digestion, is circumvented.

The rate determining factor for the absorption of drug in the vehicle is not the enzymatic metabolism of triglycerides but rests primarily in the breakdown of the fat globules into micro particles since the enzymes (lipases) act mainly at the surface of the fat globules.

In the preconcentrates of the invention, the amounts of the components, in percent by weight, are as follows:

Component	General	Usual	Preferred
Active pharmaceutical	1-12%	2.5-10%	7-10%
Oil phase	20-80%	30-60%	25-40%
Surfactant	20-40%	25-60%	40-50%
Hydrophilic phase	10-60%	20-50%	25-30%

In the microemulsions, the weight percent of hydrophilic phase is generally up to about 75%, most usually from 15 to 50%, and preferably from 35 to 50%.

The compositions can consist only of the components described, or they can contain other substances. For example, in order to prevent phase is generally up to about 75% most usually from 15 to 50%, and preferably from 35 to 50%.

The compositions can consists only of the components described, or they can contain other substances. For example, in order to prevent oxidation/ rancidification of the natural oils, an antioxidant, e.g. ∝-tocopherol can be used. Propyl gallate may be used as an alternative.

In order that the invention may be more fully understood, the following examples are given by way of illustration only.

Examples 1-5

Microemulsions of the invention are made of the compositions indicated, by dissolving the cyclosporin A in the oils and then forming the oil-in-water emulsions. The procedure was:

(a) dissolve the cyclosporin A in the mixture of oils with slight warming and under stirring to obtain a clear yellow liquid. Confirm the complete dissolution of the drug by microscopy;

(b) add the surfactant with stirring;

(c) add the hydrophilic phase with stirring; and

(d) add the ∞-tocopherol and mixed thoroughly.

Example 1

Preparation of microemulsion for administration in Soft Gelatine capsules:

Components	mg/capsule
Capryol 90	130
Castor oil	130
Polyoxyl-40 hydrogenated castor oil	400
∝-tocopherol	10
Propylene glycol	200
Cyclosporin A	100

Example 2

Preparation of microemulsion for administration as oral solution:

Component	mg/capsule
Capryol 90	150
Masine	125
Polysorbate-80 (Tween 80)	425
∝-tocopherol	10
Transcutol	225
Cyclosporin A	100

Example 3:

Preparation of microemulsion for administration as oral solution:

Components	mg/capsule
Capryol 90	275
Polyoxyl-40 hydrogenated castor oil	425
∝-tocopherol	10
Propylene glycol	225
Cyclosporin A	100

Example 4:

Preparation of microemulsion for administration as oral solution:

Components	mg/capsule
Capryol 90	130
Lauroglycol 90	130
Polysorbate 80 (Tween 80)	400
∝-tocopherol	10
Propylene glycol	200
Cyclosporin A	100

Example 5:

Preparation of microemulsion for administration as oral solution:

Components	%
Capryol 90	14
Maisine	15
Polyoxyl-40 hydrogenated castor oil	45
∝-tocopherol	1
Transcutol glycol	25
Cyclosporin A	10

The oral solution which is filled into bottles are administered using a syringe or more preferably with the aid of a metered dose pump with a dropper actuator.

The compositions described in Examples 1 to 5 were subjected to stability examinations under accelerated conditions of temperature and humidity. The solutions were stored at RT (25°C ± 2°C). Ref 40°C-80% RH and 45°C, after filling into flint glass vials.

Simultaneously with the examination of solutions prepared according to the process of the invention, the stability of the commercially available Sandimmun Neoral capsules containing 100mg cyclosporin A per capsule was also examined.

The quantitative determination of cyclosporin A was performed by using HPLC method under the conditions noted below.

Pump	Water -510 HPLC pump
Detector	Waters -484 tunable absorbance detector
Injector	Water -715 ultra wisp sample processor
Column	4.6mm x 25cm column with L 16 packing
Thermostat	70° - For capsules 50° - For oral solution
Eluant	Filtered and degassed mixture of acetronitrile water, Methanol and phosphoric acid (550:400:50:0.5)
Flow rate	1ml/min of the eluant
Integrator	Waters -746

It was observed from the above examination that the stability of solutions prepared according to the process of invention did not differ from the stability of the commercially available composition.

We Claim:

1. A pharmaceutical composition in the form of a stable oil-in-water microemulsion, consists essentially of:
   (a) water-insoluble pharmaceutically active material:
   (b) C8 to C20 propylene glycol esters of fatty acids of vegetable oils and glyceryl esters of fatty acids or fatty acid vegetable oil glycerides;
   (c) Surfactant; and
   (d) A hydrophilic phase;

2. A composition as claimed in claim 1, wherein component (a) is selected from the group consisting of a cyclosporin, or another water-insoluble peptide, or a water-insoluble antimicrobial or antineoplastic substance or mixtures thereof.

3. A composition as claimed in claim 1, wherein component (a) is selected from the group consisting of cyclosporin A, dihydrocyclosporin C, cyclosporin D or dihydrocyclosporin D, or desmopresin, calcitonin, insulin, leuprolide, erythropoetin, a cephalosporin, vincristine, vinblastine, taxol or etoposide or mixtures thereof.

4. A composition as claimed in claim 1, wherein component (b) the glycerides are of C 12 to C 18 fatty acids.

5. A composition as claimed in claim 1, wherein component (c) the said surfactant is selected from the group consisting of polyoxyl 40 hydrogenated castor oil, polyoxyethylene-sorbitan monooleate, polyoxyethylene-sorbitan monopalmitate, polyoxyethylene-sorbitan monolaurate or polyoxyethylene-sorbitan monosterate or mixtures thereof.

6. A composition as claimed in claim 1, wherein the weight ratio of component (a) to component (b) is from 1:1 to 1:10.

7. A composition as claimed in claim 1 wherein the weight ratio of component (a) to said phospholipid is from 1: 0.5 to 1:5:0.

8. A composition as claimed in claim 1, wherein the weight ratio of component (a) to said surfactant is from 1:1 to 1:5.0.

9. A process as claimed in claim 7, wherein a preconcentrate composition is mixed with component (d).

10. A soft gelatine capsule or oral administration fluid comprises a composition as claimed in claim 1 and formulated in a form for oral administration.

11. An oral administration composition which comprises a composition as claimed in claim 1 and formulated in a form for oral administration.

12. A composition as claimed in claim 1, wherein component (a) is selected from the group consisting of a cyclosporin, or another water-insoluble peptide, or a water insoluble antimicrobial or antineoplastic substance or mixtures thereof.

13. A composition as claimed in claim 11, wherein component (a) is selected from the group consisting of cyclosporin A, dihydrocyclosporin C, cyclosporin D or dihydrocyclosporin D, or desmopresin, calcitonin, insulin, leuprolide, erythropoetin, a cephalosporin, vincristine, vinblastine, taxol or etoposide or mixtures thereof.

14. A pharmaceutical composition for oral administration which comprises a stable oil-in-water microemulsion of:

(a) water-insoluble pharmaceutically active cyclosporin;

(b) C8 to C20 fatty acid mono, -di, or tri-glycerides from vegetable oil, or any mixture of two or more thereof;

(c) a phospholipid and another surfactant; and

(d) a hydrophilic phase;

wherein composition is made by first forming a preconcentrate by directly dissolving component (a) in component (b), the preconcentrate containing component (c), and then mixing the preconcentrate with the hydrophilic phase;

15 A composition as claimed in claim 14, wherein component (a) is cyclosporin A, dihyrocyclosporin C, cyclosporin D or dihydrocyclosporin D; in component (b), the glycerides are formed

from C12 to C18 fatty acids; and in component (c), said surfactant is one of polyoxyl 40 hydrogenated castor oil, polyoxyethylene-sorbitan monooleate, polyoxyethylene-sorbitan monopalmitate, polyoxyethylene-sorbitan monolaurate or polyoxyethylene-sorbitan monosterate.

16 A composition as claimed in claim 15, wherein the component (b) the said vegetable oil is whole castor oil, C8 to C20 propylene glycol esters of fatty acids of vegetable oils and glyceryl esters of fatty acids or fatty acid vegetable oil glycerides, or is derived therefrom.

17 A composition as claimed in claim 16, wherein the weight ratio of component (a) to component (b) is from 1:1 to 1:10; the weight ratio of component (a) to said phospholipid is from 1:0.5 to 1:5.0; and the weight ratio of component (a) to said surfactant is from 1:1 to 1:5.0.

18 A composition as claimed in claim 17 in the form of a soft gelatine capsule or an oral administration fluid.

19 A method of making pharmaceutical composition in the form of a stable oil-in-water microemulsion, as claimed in claims 1-19 comprises the steps of: first forming a preconcentrate by directly dissolving water-insoluble pharmaceutically active material in C8 to C20 propylene glycol esters of fatty acids of vegetable oils and

glyceryl esters of fatty acids or fatty acid vegetable oil glycerides, where the said water-insoluble pharmaceutical active material remains with tendency to form solid microfine active material being totally absent with no precipitation of said active material taking place.

INTERNATIONAL SEARCH REPORT

Inte...tional Application No
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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/107 A61K9/48 A61K38/13

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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X	WO 99 44584 A (NOVARTIS ERFINDUNGEN VERWALTUN ;HAEBERLIN BARBARA (CH); NOVARTIS A) 10 September 1999 (1999-09-10) page 2, line 13 -page 3, line 2 page 3, line 27 -page 4, line 3 page 4, line 13 -page 4, line 16 page 15, line 8 -page 15, line 19 page 21, line 12 -page 21, line 22 page 23, line 13 -page 23, line 14 page 40, line 28 -page 40, line 29 example X --- -/--	1-6,8-13

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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Date of the actual completion of the international search	Date of mailing of the international search report
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Name and mailing address of the ISA	Authorized officer
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International Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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